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Original Article

Neonatal Vitamin D Levels in Relation to Risk of Overweight at 7 Years in the Danish D-Tect Case-Cohort Study

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Keywords

Vitamin D, pregnancy · Dried blood spots · Childhood overweight · BMI · Epidemiology · Case-cohort study

Abstract

Background: Vitamin D level in pregnancy may be associated with risk of overweight in the offspring later in life. ***Methods:*** In a case-cohort study based on Danish biobanks and registers we examined the association between 25-hydroxy-vitamin D (25(OH)D) level at birth and overweight at 7 years. Cases of overweight (n = 871) were randomly selected among 7-year-old children from the Copenhagen School Health Records Register (CSHRR) with a BMI above the 90th percentile. The cohort (n = 1,311) was a random sample selected among all Danish children born during the same period. Neonatal 25(OH)D was measured in dried blood spots. ***Results:*** 25(OH)D_3 exhibited the expected seasonal variation. Median level of 25(OH)D_3 was 20.6 (11.9–33.3) nmol/l in the overweight group and 23.4 (13.5–34.3) nmol/l in the cohort. We found no association between neonatal 25(OH)D_3 level and risk of overweight at age 7 years, neither in the crude model (OR (CI) 1.00 (0.99; 1.00)) nor in a model adjusted for maternal ethnicity, educational level, civil status, parity, season and year of birth, and offspring ponderal index (OR (CI) 1.00 (0.99; 1.01)). ***Conclusion:*** Risk of overweight at 7 years of age was not associated with vitamin D level at birth.

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Introduction

There is increasing evidence that exposures during fetal life may program health of the individual later in life. Vitamin D deficiency is one of these fetal exposures that have been proposed to influence later health, and the list of potential programming effects includes preterm delivery [1], size at birth [2], impaired bone health in the offspring [3], asthma [4], and type 1 diabetes [5] among others.

Another potential programming effect of fetal vitamin D deficiency is increased risk of adiposity in the offspring [6–9]. Although there is conflicting results [10], vitamin D has been proposed to inhibit the early phase of differentiation of pre-adipocytes to mature adipocytes and to reduce fat accumulation [11]. The association between fetal vitamin D exposure and later risk of adiposity has been examined in two studies [8, 12]. One study found increased odds of overweight in 1-year-old children if the mother was vitamin-D-deficient in early pregnancy [8], but there was no association at 4 years. The other study found a direct association between neonatal vitamin D level and odds of overweight at 35 years of age [12].

Other measures of body size and composition have been investigated in relation to fetal vitamin D exposure and include weight, height, BMI, fat mass, and fat-free mass. Most studies report an inverse association between fetal vitamin D exposure and later body size [6, 7, 9] if any [13, 14], but direct associations have also been found [9]. Common for all studies is that they have investigated various outcome measures at several ages and only found associations with vitamin D in few of the analyses. Thus, there is no obvious pattern in the associations of body size measures with vitamin D.

The aim of the present study was to investigate the association between neonatal 25-hydroxy-vitamin D (25(OH)D) levels and subsequent risk of overweight at the age of 7 years. Based on the theory that vitamin D has the potential to inhibit adipocyte differentiation [10, 11] we hypothesized that low vitamin D level at birth was associated with increased risk of childhood overweight.

Material and Methods

Study Population

Cases were selected from the Copenhagen School Health Records Register (CSHRR) [15]. The CSHRR contains information on height and weight at school entry (approximately 7 years of age) for all children who went to school in the Copenhagen municipality born from 1930 to 1991 and includes 381,110 records. School doctors and nurses measured height to the nearest 0.5 cm and weight to the nearest 100 g. BMI was calculated for each child as weight (kg) / height^2 (m).

From 1981 onwards, blood samples taken from heel pricks have been stored as dried blood spots (DBS) for all newborns in Denmark in the Danish Newborn Screening Biobank [16]. Thus children in the CSHRR born between 1981 and 1991, who had height and weight measures at age approximately 7 years (age range 6–8 years) were eligible for the study. BMI is positively associated with age, so we adjusted BMI for age to control for the fact that the children were not measured at exactly age 7 years.

The internal 90th percentile of the sex-specific BMI distributions for children in the CSHRR born between 1981 and 1991 was used to define overweight. From the top 10% of BMIs we randomly selected 600 girls and 600 boys.

As controls we randomly selected a sub-cohort among all children born in Denmark from 1981 to 1991 (n = 1,718). The cohort was selected to facilitate studies of several outcomes besides overweight, and it was therefore selected from the entire Danish population rather than from the Copenhagen area, as the cases.

Assessment of Vitamin D Level on DBS

Liquid chromatography tandem mass spectroscopy (LC-MS) was used to assess 25(OH)D_2 and 25(OH)D_3 from neonatal DBS supplied by the Danish National Biobank. For each individual, a 3.2 mm punch was

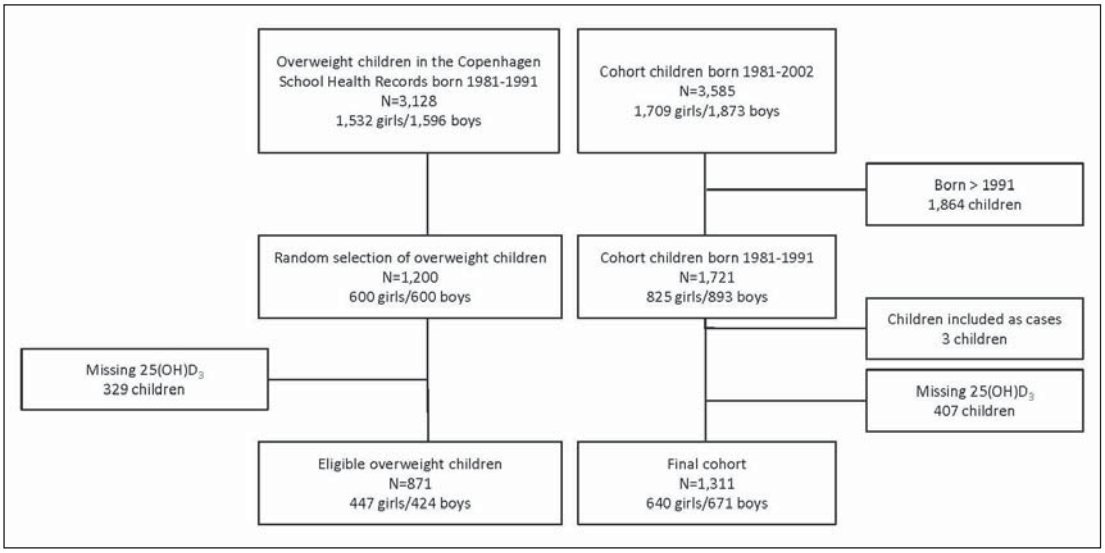

Fig. 1. Flow chart of the study population.

taken from the DBS. Calibration was conducted by using commercially available calibrators (Perkin Elmer, Waltham, MA, USA). To control the quality of the analyses two sets of commercially available controls (Perkin Elmer) in three different concentration levels were analyzed before and after project samples within each batch. In addition, native full blood from a healthy volunteer was spotted unto filter paper and analyzed before and after projects samples. The maximum %cv was 15 for the project. The LC-MS system consisted of an Aria TLX2 system (Thermo Fisher Scientific, Waltham, MA, USA) with two Agilent 1100 binary pumps and two Agilent Quaternary pumps (Agilent, Santa Clara, CA, USA) connected to a Thermo TSQ Ultra triple quadrupole mass spectrometer equipped with an ESI ion source. Online extraction was performed using a Cyclone P 0.5 × 50 mm turbo flow column (Thermo Fisher Scientific), and analytical separation was achieved using Hypersil gold 50 × 2.1mm, 3 µm revered phase column (Thermo Fisher Scientific). The 25(OH)D levels were reported in nmol/l and corrected to reflect sera levels using the hematocrit fraction for capillary blood (1–1/0.61) [17]. We excluded measures of $25(OH)D_2$ levels from the main analyses because the majority (84%) had levels below the lower limit of quantification 3 nmol/l. We included all measured $25(OH)D_3$ levels, also the ones below the lower limit of quantification of 4 nmol/l (17%).

Covariates

The civil registration number was used to obtain child characteristics at birth and maternal background information from the Danish Medical Birth Register [18] and from Statistics Denmark [19].

The included covariates were as follows: Maternal age at birth (continuous (years)), maternal highest obtained education (school, high school, and university), parity (continuous (number of previous births)), and maternal ethnicity (Danish, Western, and non-Western). Season of birth (winter (November to January), spring (February to April), summer (May to July), and fall (August to October) [20]), birth weight (continuous (kg)), birth length (continuous (cm)), ponderal index (PI; (birth weight (g) × 100) / (birth length (cm))^3 continuous), gestational age (continuous (weeks)), and year of birth (continuous (year)).

Ethical Approval

The Danish Data Protection Agency gave permission for data retrieval and merging (J. no.: 2012–41–41156). Permission to access and analyze the DBS was granted by the Ethical Committee of the Capital Region of Denmark (J. no.: H-3–2011–126) and the Danish Neonatal Screening Biobank Steering Committee.

Statistical Analyses

Differences between cases and the cohort were checked using chi-square test and t-test. $25(OH)D_3$ distribution within covariate strata was checked using Kruskal-Wallis and Wilcoxon signed rank tests

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Table 1. Characteristics of the study population

	Cases	Cohort	p value
N	871	1,311	
$25(OH)D_3$ (Median (Q1–Q3))	20.6 (11.9–33.3)	23.4 (13.5–34.3)	0.004
Sex n (%)			0.3
Girls	447 (51)	640 (49)	
Boys	424 (49)	671 (51)	
Season of birth n (%)			0.02
Winter	234 (27)	314 (24)	
Spring	182 (21)	313 (24)	
Summer	247 (28)	320 (24)	
Fall	208 (24)	364 (28)	
Maternal age (mean (SD)), years	27.3 (5.2)	27.3 (4.9)	0.8
Maternal education n (%)			0.005
School	345 (45)	478 (38)	
High school	276 (36)	532 (43)	
University	142 (19)	234 (19)	
Missing	108	67	
Parity n (%)			0.002
1. child	461 (53)	596 (46)	
2. child or more	410 (47)	693 (54)	
Missing	0	22	
Maternal ethnicity n (%)			<0.001
Danish	640 (73)	1,227 (94)	
Western	26 (3)	22 (2)	
Non-western	205 (24)	52 (4)	
Missing	0	10	
Birth weight (mean (SD)), g	3,492 (577)	3,439 (567)	0.04
Birth length (mean (SD)), cm	51.7 (2.4)	51.6 (2.6)	0.5
Ponderal index (mean (SD))	2.53 (0.24)	2.49 (0.23)	0.0002
Gestational age (mean (SD)), days	39.5 (1.8)	39.6 (1.7)	0.2
Civil status n (%)			0.02
Married	496 (57)	766 (60)	
Not married	314 (36)	469 (37)	
Divorced	55 (6)	44 (3)	
Missing	6	32	

because of the non-normal distribution. We used logistic regression to estimate odds ratio (OR) and 95% confidence intervals (95% CI) in order to analyze the association between neonatal $25(OH)D_3$ level and odds of overweight at 7 years of age. Analyses were performed crude and adjusted for a priori specified covariates.

$25(OH)D_3$ was modeled in three different ways; continuously (nmol/l), by quintiles (based on the distribution in the cohort), and by clinical categories (deficiency (<25 nmol/l), suboptimal (25–50 nmol/l), and optimal (>50 nmol/l)). The two latter models were employed to investigate potential deviation from linearity.

Sensitivity analyses included analyses of total 25(OH)D (sum of $25(OH)D_2$ and $25(OH)D_3$), analyses excluding $25(OH)D_3$ levels below the detection limit and analyses excluding children of non-western origin. Further sensitivity analyses included use of season-specific quintiles of vitamin D level to control for seasonality in vitamin D levels [21].

We restricted the cohort to individuals who were in the CSHRR to investigate if the fact that cases were sampled from the Copenhagen School Health Records Register while the cohort was sampled from the entire Danish population may have introduced selection bias.

All statistical analyses were performed in Stata (version 14) [22]. A two-sided p value < 0.05 was considered significant.

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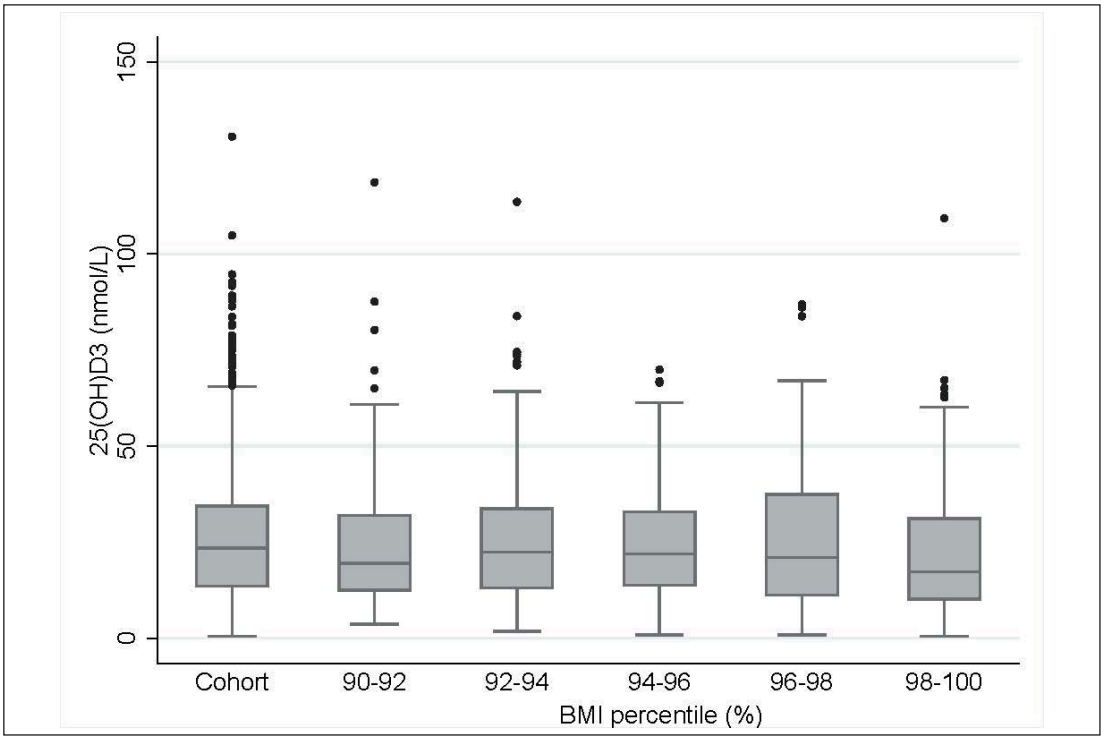

Fig. 2. Serum 25(OH)D_3 distribution for children in the cohort and overweight cases according to BMI percentiles (percentile (BMI) 90–92 (17.9–18.6), 92–94 (18.6–18.9), 94–96 (18.9–19.6), 96–98 (19.6–20.7), 98–100 (20.7–26.4)).

Results

The flow of the study population can be seen in figure 1, and characteristics of the study population can be seen in table 1.

The median level of 25(OH)D_3 was 20.6 (interquartile range 11.9–33.3) nmol/l in the overweight group and 23.4 (interquartile range 13.5–34.3) nmol/l in the cohort. Boxplots of the 25(OH)D_3 distribution can be seen in figure 2 for the cohort and the overweight children stratified by BMI percentile. Median 25(OH)D_3 decreased with increasing BMI but not significantly ($p = 0.09$). In the overweight group 60% had deficient vitamin D levels (<25 nmol/l) and in the cohort 55% ($p = 0.03$).

In table 2 the 25(OH)D_3 distribution within covariate strata can be seen. 25(OH)D_3 level fluctuated significantly with season of birth for both the cases and the cohort. The highest median level was seen in summer followed by fall. The lowest median level was in spring which was only a little lower than in winter. 25(OH)D_3 increased significantly with maternal age and maternal educational level for both the cases and the cohort (table 2). There was an inverse association between 25(OH)D_3 and parity. In the cases there was a significant inverse association between 25(OH)D_3 and gestational age. Non-western children had the lowest 25(OH)D_3. In the cases there was a significant difference in 25(OH)D_3 according to maternal civil status where the children with married mothers had the lowest level.

There was a significantly increasing trend in 25(OH)D_3 across the study period in the cohort ($p < 0.001$), but not in the overweight group ($p = 0.1$). There was no difference in 25(OH)D_3 between children living in Copenhagen compared to those in the remaining part of Denmark ($p > 0.2$).

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Table 2. 25(OH)D_3 levels (median (inter quartile range)) according to covariates for the overweight cases and the cohort

	N	Cases			p value	N	Cohort			p value
		median	Q1	Q3			median	Q1	Q3	
Sex					0.4					0.4
Boys	424	18.9	11.7	32.3		671	24.1	14.0	34.0	
Girls	447	21.4	12.0	34.6		640	22.8	13.0	34.9	
Season of birth					0.0001					0.0001
Winter	234	17.5	10.2	25.8		314	18.8	12.1	28.0	
Spring	182	15.4	8.9	24.7		313	17.7	10.9	26.2	
Summer	247	26.7	14.8	38.8		320	28.5	17.7	42.4	
Fall	208	25.4	15.4	39.5		364	28.0	17.5	38.9	
Maternal age					0.0001					0.003
<30 years	573	18.7	11.0	31.6		912	22.4	12.8	34.0	
≥30 years	298	23.2	14.8	37.4		399	25.2	16.3	35.1	
Maternal education					0.0001					0.0001
School	345	18.3	10.1	30.5		478	20.8	12.1	32.3	
High school	276	22.0	14.5	34.0		532	24.9	14.8	35.6	
University	142	27.2	16.9	44.9		234	26.1	17.3	38.8	
Parity					0.001					0.004
1. child	461	22.3	13.4	35.3		596	24.3	14.5	36.6	
2. child or more	410	18.5	10.1	31.7		693	22.0	12.9	32.8	
Birth weight					0.07					0.6
<2.5 kg	35	31.6	12.4	49.9		54	22.6	16.3	41.8	
2.5–4.5 kg	794	20.0	11.5	32.9		1195	23.3	13.3	34.2	
≥4.5 kg	40	21.5	14.7	31.9		38	25.3	15.7	33.3	
Ponderal index					0.8					0.8
Low	73	22.8	12.5	33.3		137	20.2	12.8	36.4	
Normal	666	20.0	11.8	33.0		1051	23.5	13.4	34.3	
High	132	20.9	11.7	34.5		123	23.7	15.7	32.6	
Gestational age					0.009					0.08
Preterm	42	31.1	14.7	50.7		49	26.2	16.0	42.4	
Early term	133	21.9	13.0	38.5		185	26.2	13.4	39.7	
Term	474	19.9	10.8	31.9		695	22.9	14.0	32.9	
Late term	132	19.4	12.2	31.0		238	22.5	12.6	33.3	
Postterm	90	17.5	12.4	29.2		134	24.0	12.3	34.8	
Civil status					0.0003					0.3
Married	496	18.4	10.5	31.7		766	23.4	13.6	34.3	
Not married	314	22.8	14.9	31.7		469	23.8	13.2	35.1	
Divorced	55	23.3	12.4	37.2		44	20.7	14.6	26.9	
Maternal ethnicity					0.0001					0.0001
Danish	640	23.0	14.4	36.6		1227	23.8	13.8	35.1	
Western	26	18.4	13.3	41.02		22	26.0	18.7	51.8	
Non-western	205	12.6	7.2	22.18		52	13.3	6.2	21.0	

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Table 3. OR (CI) of overweight at age 7 years according to neonatal 25(OH)D_3 levels

	OR (CI) of overweight at 7 years					
	crude			adjusted*		
	OR	CI		OR	CI	
Continuous 25(OH)D_3, nmol/l	1.00	0.99	1.00	1.00	0.99	1.01
Quintiles limits, nmol/l						
Q1 (<12.0)	1.54	1.18	2.02	1.17	0.85	1.61
Q2 (12.0–19.6)	1.28	0.97	1.69	1.28	0.94	1.75
Q3 (19.6–28.0)	1	1	1	1	1	1
Q4 (28.0–40.8)	0.99	0.74	1.32	1.11	0.81	1.52
Q5 (>40.8)	1.12	0.85	1.49	1.17	0.85	1.60
Clinical categories, nmol/l						
<25	1.09	0.80	1.48	0.99	0.70	1.40
25–50	0.84	0.61	1.16	0.90	0.64	1.29
>50	1	1	1	1	1	1

*Adjusted for maternal ethnicity, educational level, civil status, parity, season and year of birth, and offspring PI.

Overall, we found no association between neonatal 25(OH)D_3 status and odds of overweight at age 7 years, neither in the crude model (OR (CI) 1.00 (0.99; 1.00)) nor in the model adjusted for maternal ethnicity, educational level, civil status, parity, season and year of birth, and offspring PI (OR (CI) 1.00 (0.99; 1.01)).

Modelling vitamin D in quintiles or in clinical categories (<25, 25–50, > 50 nmol/l) did not reveal any non-linear associations table 3.

Sensitivity analyses of pooled 25(OH)D_2 and 25(OH)D_3 showed no association between total vitamin D level and overweight at 7 years (OR (CI) crude 0.99 (0.99; 1.00) and adjusted 1.00 (0.99; 1.00)). Excluding the observations with 25(OH)D_3 levels below the lower limit of quantification did not change the results (OR (CI) crude 1.00 (0.99; 1.01) and adjusted 1.00 (0.99; 1.01)). Restricting the analyses to children with Danish and western mothers showed no association between 25(OH)D_3 and overweight at 7 years (OR (CI) crude 1.00 (1.00; 1.01) and adjusted 1.00 (0.99; 1.01)). Sensitivity analyses using only the cohort individuals in the CSHRR did not change the results (OR (CI) crude 0.99 (0.98; 1.00) and adjusted 1.00 (0.98; 1.01)) and showed no indications of selection bias. None of the sensitivity analyses showed any association between vitamin D and overweight at 7 years when allowing the association to be non-linear (data not shown).

Discussion

In the present study we found no association between neonatal vitamin D level and risk of overweight at age 7 years. 25(OH)D_3 was not associated with risk of overweight neither in models assuming a linear association nor in models allowing the association to be non-linear. Including 25(OH)D_2 in analyses of total 25(OH)D showed no association with overweight either. The 95% CIs for the ORs were very narrow in all analyses, and we see this precision as an indication that the results are not incidental null findings.

Two other studies have looked specifically at the risk of overweight or obesity rather than the continuous distribution of BMI or other measures of body size [8, 12], and they show

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inconclusive results. One study reported an increased risk of overweight (defined by the 85th percentile) at age 1 year, but not at 4 years, among children of mothers with vitamin D deficiency in gestational week 14 [8]. The other found a significant direct association between neonatal vitamin D level and overweight at 35 years of age and obesity in women only [12]. They did not include measures of body size during childhood. The prevalence of overweight is higher in adulthood than in childhood [23], which means that not all children have become overweight yet at 7 years of age. Had we defined overweight at an older age in childhood or adulthood the number of cases would have been higher. However, overweight in childhood is a strong predictor of overweight in adulthood and a risk factor for a long list of diseases [23, 24].

Studies of other measures of body size and composition have also yielded conflicting results. Fat mass and body fat percentage were found to be either inversely associated with fetal vitamin D exposure [6, 7, 9] or to have no association with fetal vitamin D exposure [9, 13]. Fat-free mass and body fat-free percentage were not associated with fetal vitamin D exposure [6, 9, 13] except in one case [9]. BMI was not associated with fetal vitamin D exposure in most studies [7–9, 13, 14], but in a few cases direct associations were found [9, 12]. No studies found associations between fetal vitamin D exposure and later weight or height [9, 13].

Contrasts between the studies included the obvious difference in outcome measures, age at follow-up ranging from 9 months of age to 35 years of age, and timing of the exposure evaluation. One previous study have measured neonatal vitamin D level directly [12], while the others have approximated fetal vitamin D level by measuring maternal vitamin D level during pregnancy at various gestational ages ranging from early pregnancy [7, 8] over mid-pregnancy[14] to late pregnancy [6, 9, 13]. The 25(OH)D_3 levels in our study were noticeably lower than the ones in the previous studies on vitamin D and body size [6–9, 12–14]. Vitamin D level fluctuates during pregnancy [25] and timing of blood sampling influences the measured level. Furthermore, offspring vitamin D levels are approximately 80% of maternal levels [26].

Overweight can be defined in many different ways, and we chose to define overweight according to BMI using the 90th percentile. Initial tests showed that the overweight children in this study were all categorized as overweight (including obese) and 27% were categorized as obese had we used the International Obesity Task Force cutoffs [27]. If the association between neonatal vitamin D level and later adiposity is only present for the obese cases, it is possible that the results would have been different had we focused on obesity rather than overweight.

One of the strengths of the present study was the use of biomarkers for the estimation of vitamin D level. Vitamin D level was measured in stored DBS, a method that has been shown to estimate 25(OH)D level accurately and to be a valid and reliable alternative to measured 25(OH)D in sera or plasma [17, 28]. However, the 25(OH)D_3 level in our population was considerably lower compared to that in a previous study of a similar population selected from the Danish Newborn Screening Biobank in the years 1981–1994 where a similar method was used in an Australian laboratory (median 25(OH)D_3 23.4 vs. 32.3 nmol/l) [29]. The difference might be a result of inter-laboratory variation which is common and expected for vitamin D [28, 30]. Another explanation could be the area of the DBS that was chosen to measure the 25(OH)D_3 level since the concentration of blood is not evenly distributed across the DBS. We standardized the sampling of the DBS so that the same area was used for all samples in our study to prevent bias. Another limitation of our method is that we used only one punch for each measurement which excluded the possibility of confirming the measured 25(OH)D level. However, the confirmation of significant seasonal variation in 25(OH)D_3 levels and variation across other covariate strata indicated that the measures can be used to rank the 25(OH)D_3 levels within the study population. Therefore, absolute 25(OH)D_3 levels should be inter-

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preted with care and the emphasis should lie upon the results based on the continuous use and ranking of $25(OH)D_3$ levels rather than the ones using the clinical cutoffs.

In this study cases were sampled from school children in Copenhagen while the cohort was sampled from the whole of Denmark. Denmark is a small country, and there are no substantial environmental differences across the country. However, the population residing the capital is different from the general Danish population in regards to ethnicity for example. To prevent confounding we have adjusted for ethnicity in our analyses and restricted analyses to children of Danish and western background. Cases were sampled from the CSHRR while the cohort was sampled from the entire Danish population. To investigate if the study design introduced selection bias, we restricted the cohort to individuals who were in the CSHRR and checked if this yielded different results. Fortunately, the risk estimates were virtually identical and showed no indications of selection bias.

Maternal body size has been associated with both offspring body size [31] and neonatal vitamin D levels [32, 33] and was therefore a potential confounder of the association between neonatal vitamin D level and later risk of overweight. It was a limitation of the study that information about maternal BMI was not available and potential confounding could not be controlled for.

In conclusion, we found no association between vitamin D level at birth and risk of overweight at 7 years of age, while previous studies have found conflicting results. Currently, the combined evidence cannot support an association between fetal vitamin D exposure and later overweight.

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Authorship

The authors’ responsibilities were as follows – BLH conceived the research idea; CBJ, ML, TIAS, and BLH designed research; ML analyzed data; CBJ performed statistical analysis; CBJ, ML, TIAS, and BLH wrote the paper; CBJ had primary responsibility for the final content. All authors read and approved the final manuscript.

Disclosure Statement

The authors declared that they have no conflicts of interest.

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